

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

<p>Inventor Application of: Ashkenazi et al.</p> <p>Serial No.: 09/903,925</p> <p>Filed: July 11, 2001</p> <p>For: SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS</p>	<p>Group Art Unit: 1647</p> <p>Examiner: Fozia Hamid</p> <p>CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on</p> <p>Date _____</p>
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DECLARATION OF AUDREY D. GODDARD, Ph.D UNDER 37 C.F.R. § 1.132

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Audrey D. Goddard, Ph.D. do hereby declare and say as follows:

1. I am a Senior Clinical Scientist at the Experimental Medicine/BioOncology, Medical Affairs Department of Genentech, Inc., South San Francisco, California 94080.
2. Between 1993 and 2001, I headed the DNA Sequencing Laboratory at the Molecular Biology Department of Genentech, Inc. During this time, my responsibilities included the identification and characterization of genes contributing to the oncogenic process, and determination of the chromosomal localization of novel genes.
3. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).

Serial No.: *

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4. I am familiar with a variety of techniques known in the art for detecting and quantifying the amplification of oncogenes in cancer, including the quantitative TaqMan PCR (i.e., "gene amplification") assay described in the above captioned patent application.

5. The TaqMan PCR assay is described, for example, in the following scientific publications: Higuchi *et al.*, Biotechnology 10:413-417 (1992) (Exhibit B); Livak *et al.*, PCR Methods Appl., 4:357-362 (1995) (Exhibit C) and Heid *et al.*, Genome Res. 6:986-994 (1996) (Exhibit D). Briefly, the assay is based on the principle that successful PCR yields a fluorescent signal due to Taq DNA polymerase-mediated exonuclease digestion of a fluorescently labeled oligonucleotide that is homologous to a sequence between two PCR primers. The extent of digestion depends directly on the amount of PCR, and can be quantified accurately by measuring the increment in fluorescence that results from decreased energy transfer. This is an extremely sensitive technique, which allows detection in the exponential phase of the PCR reaction and, as a result, leads to accurate determination of gene copy number.

6. The quantitative fluorescent TaqMan PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression. Amplification of protooncogenes has been studied in a variety of human tumors, and is widely considered as having etiological, diagnostic and prognostic significance. This use of the quantitative TaqMan PCR assay is exemplified by the following scientific publications: Pennica *et al.*, Proc. Natl. Acad. Sci. USA 95(25):14717-14722 (1998) (Exhibit E); Pitti *et al.*, Nature 396(6712):699-703 (1998) (Exhibit F) and Bieghe *et al.*, Int. J. Cancer 78:661-666 (1998) (Exhibit G), the first two of which I am co-author. In particular, Pennica *et al.* have used the quantitative TaqMan PCR assay to study relative gene amplification of WISP and c-myc in various cell lines, colorectal tumors and normal mucosa. Pitti *et al.* studied the genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer, using the quantitative TaqMan PCR assay. Bieghe *et al.* used the assay to study gene amplification in breast cancer.

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7. It is my personal experience that the quantitative TaqMan PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

8. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Jan. 16, 2003

Date

Audrey D. Goddard

Audrey D. Goddard, Ph.D.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : *

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Examiner : *

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) I hereby certify that this correspondence
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) deposited with the United States Postal
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Assistant Commissioner for Patents
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Dear Sir:

I, Audrey D. Goddard, Ph.D. do hereby declare and say as follows:

1. I am a Senior Clinical Scientist at the Experimental Medicine/BioOncology, Medical Affairs Department of Genentech, Inc., South San Francisco, California 94080.
2. Between 1993 and 2001, I headed the DNA Sequencing Laboratory at the Molecular Biology Department of Genentech, Inc. During this time, my responsibilities included the identification and characterization of genes contributing to the oncogenic process, and determination of the chromosomal localization of novel genes.
3. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).
4. I am familiar with a variety of techniques known in the art for detecting and quantifying the amplification of oncogenes in cancer, including the TaqMan™ PCR assay.
5. The TaqMan™ PCR assay is described, for example, in the following scientific publications: Higuchi *et al.*, *Biotechnology* 10:413-417 (1992) (Exhibit B); Livak *et al.*, *PCR Methods Appl.*, 4:357-362 (1995) (Exhibit C); and Heid *et al.*, *Genome Res.* 6:986-994 (1996)

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(Exhibit D). Briefly, the assay is based on the principle that successful PCR yields a fluorescent signal due to Taq DNA polymerase-mediated exonuclease digestion of a fluorescently labeled oligonucleotide that is homologous to a sequence between two PCR primers. The extent of digestion depends directly on the amount of PCR, and can be quantified accurately by measuring the increment in fluorescence that results from decreased energy transfer. This is a sensitive technique, which allows detection in the exponential phase of the PCR and, as a result, leads to accurate determination of initial genomic sequence copy number.

6. The quantitative fluorescent TaqMan™ PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression. Amplification of protooncogenes has been studied in a variety of human tumors, and is generally considered as having etiological, diagnostic and prognostic significance. This use of the TaqMan™ PCR assay is exemplified by the following scientific publications: Pennica D, *et al.*, *Proc. Natl. Acad. Sci. USA* 95(25): 14717-14722 (1998) (Exhibit E); Pitti *et al.*, *Nature* 396(6712): 699-703 (1998) (Exhibit F); and Bieche, *et al.*, *Int. J. Cancer* 78:661-666 (1998) (Exhibit G), the first two of which I am co-author. In particular, Pennica *et al.* has used the TaqMan™ PCR assay to study relative gene amplification of WISP and *c-myc* in various cell lines, colorectal tumors, and normal mucosa. Pitti *et al.* studied the genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer, using the TaqMan™ PCR assay. Bieche *et al.* used the assay to study gene amplification in breast cancer.

7. It is my personal experience that TaqMan™ PCR is technically sensitive enough to detect at least 2-fold gene amplifications relative to control. It is further my considered scientific opinion that ~~4-to~~ 4-fold amplification of a gene is significant, and that at least 4-fold amplification of a gene in a tumor sample relative to control in a significant proportion of tumors is an indication that the gene is likely to be associated with malignancy. Accordingly, a gene identified as amplified at least 4-fold by the TaqMan™ technique may find utility in the diagnosis of cancer or to monitor cancer development, or the efficacy of cancer therapy.

8. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

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States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date

Audrey D. Goddard, Ph.D.

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